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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant : Timothy H. Bestor

Serial No. : 09/051,013 Examiner: D.J. Steadman

Filed : October 9, 1998 Group Art Unit: 1652

For : CHIMERIC DNA-BINDING/ DNA METHYLTRANSFERASE NUCLEIC ACID AND POLYPEPTIDE AND USES THEREOF

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January 20, 2004

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Sir:

**PRELIMINARY COMMUNICATION**

This Preliminary Communication is submitted in order to address the remarks made in the December 10, 2003 Advisory Action issued in connection with the above-identified patent application. Applicant filed a Notice of Appeal on November 17, 2003, making an Appeal Brief due January 17, 2004. However, since January 17, 2004 falls on a Saturday, and Monday, January 19, 2004 is a Federal holiday, an Appeal Brief is due the following business day, January 20, 2004. In lieu of filing an Appeal Brief, applicant is filing a Request for Continued Examination herewith. Accordingly, this Communication is being timely filed.

## REMARKS

Claims 1-8, 10-15, 18, 24-26, and 42-46 are pending. Claims 9, 16-17, 19-23, 27-41, and 47 have been canceled without prejudice. No claims have been amended or canceled herein. Thus, claims 1-8, 10-15, 18, 24-26 and 42-46 remain pending and under examination.

In view of the arguments set forth below, applicant maintains that the Examiner's remarks made in the December 10, 2003 Advisory Action have been fully addressed, and the rejections made in the May 16, 2003 Final Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw the outstanding rejections.

### Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 1-8, 10-15, 18, 24-26, and 42-46 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

In response to the Examiner's rejection, applicant maintains that the specification adequately describes the claimed invention for reasons of record and for the additional reasons set forth below.

The burden is on the Examiner to show by a preponderance of the evidence why a person skilled in the art would not recognize in applicant's disclosure a description of the

invention defined by the claims. M.P.E.P. §2163.04. Applicant maintains that the Examiner has failed to meet this burden.

Specifically, the Examiner alleges that the examples provided in the instant specification are not representative of the genus of claimed chimeric proteins. Applicant understands the Examiner's opinion to be based upon the assertion that the claims encompass a genus of "substantial variation" and that this variation is allegedly not represented by the number of examples in the specification.

In response, applicant first notes that what constitutes a 'representative number' is inversely related to the skill and knowledge in the art. M.P.E.P. §2163. The knowledge and skill in the art of the invention is indisputably high. Furthermore, the variation in the claimed genus of chimeric proteins arises from the combination of known proteins in the instant chimeras. Applicant maintains that the examples provided in the specification are representative of this variation, given the knowledge of methyltransferases, DNA binding proteins, and molecular cloning in the prior art. In support of this position, applicant points out that the description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. M.P.E.P. §2163. Thus, it is not necessary for the specification to teach the structures of all chimeras comprising a "DNA methyltransferase" and a "DNA binding protein" in order to satisfy the written description requirement. All that is required is that the specification describe the invention in such clear and precise terms as to convey to one of skill in the art that which constitutes the

invention. Applicant maintains that the specification, in view of the knowledge and high level of skill in the art, adequately describes the claimed chimeras.

Contrary to the Examiner's assertion at page 4 of the Advisory Action, the particular structure of the component proteins of the instant chimeras need not be explicitly set forth in the specification. Only a generalized structure, namely that of a chimeric protein comprised of a methyltransferase tethered to a DNA binding protein, is required for one of skill to know what applicant regards as the invention. This is because one of skill could easily envision any particular chimeric protein of the claimed genus given the teachings of the specification.

The Examiner's rejection is also based in part on an alleged lack of written description concerning the structure of the particular mutations that comprise the full genus of the instant chimeras. However, it is well-recognized in the art that the identity of a particular mutation need not be known in order to make and use a particular mutant protein, as described in the specification in Examples 1 and 3. Thus, such information also need not be explicitly set forth.

In summary, applicant maintains that one of skill in the art would recognize from the teachings of the instant specification that applicant was in possession of the claimed invention.

The Examiner also rejected claims 1-8, 10-15, 18, 24-26, and 42-46 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to allow one skilled in the

relevant art to which it pertains to make and/or use the invention commensurate in scope with the claims.

In response, applicant respectfully traverses for the reasons of record and for the additional reasons set forth below.

The Examiner alleged that the specification fails to enable the broad scope of the claims. Applicant points out that "[t]he presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure ... to make a valid rejection, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims." M.P.E.P. 2164.02. Applicant maintains that given the knowledge in the art of DNA methyltransferases, DNA binding proteins, and chimeric proteins, in combination with the guidance of the instant specification, particularly Examples 1 and 3, one of skill would expect to be able to make and use the entire scope of the claimed chimeras.

The Examiner's assertion that the specification fails to provide the necessary guidance for making the claimed invention is based in part on an alleged lack of written description regarding specific mutations that would produce a methyltransferase having the desired activity for use in the claimed chimeric protein. However, such guidance is provided in detail in the specification, particularly in Example 1. As noted previously, no knowledge of the specific mutations which produce the desired activity is required to make and use the methyltransferase. Specifically, in Example 1 the specification teaches a novel selection method which is

combined with the art-recognized technique of random mutatgenesis to produce a methyltransferase having the desired activity. The Examiner has failed to state why one of skill would not expect to be able to extrapolate from applicant's example across the entire scope of the claims. Applicants maintain that nothing more than routine experimentation is required to make a methyltransferase customized to methylate only specific sites of a given promoter sequence according to the teachings in the specification. For example, extrapolation from the teaching of M.SssI in Example 1 requires only the construction of a set of primers for random mutatgenesis of the methyltransferase of choice. Such primer construction is within the routine knowledge and skill in the art.

The Examiner also alleged a lack of guidance regarding DNA binding proteins that would bind a specific DNA promoter sequence. To the extent that the claimed chimera comprises a known DNA binding protein with known sequence specificity, such as the LexA protein of Example 1, the Examiner's objection is without merit, since the specification need not teach that which is known in the art.

To the extent that the DNA binding protein consists of a mutated DNA binding protein selected for its binding specificity to a predetermined sequence, as taught in Example 3, applicant notes that the making of such DNA binding proteins was known in the prior art (see for example Desjarlais and Berg, 1993, Rebar and Pabo, 1994, and Wu et al, 1994, of record). As what was known in the art need not be described in detail in the specification in this case, applicant maintains that the guidance given in Example 3 for making a DNA binding protein which binds selectively to a

predetermined sequence is sufficient to enable one of skill to make and used the claimed chimeras.

The Examiner further alleged at page 6 of the Advisory Action that there exists a high degree of unpredictability for making the entire scope of the claimed invention. The Examiner's assertion with respect to the sufficiency of the guidance and examples provided in the specification was discussed above. The Examiner further alleged that the random mutagenesis described in Examples 1 and 3 amounts to undue experimentation because it is unpredictable as to whether it will be successful and further because the amount of experimentation required is allegedly large.

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. M.P.E.P. §2164.01. As acknowledged by the Examiner, random mutagenesis is a technique widely practiced in the art. It is routinely used to generate proteins with desirable characteristics. The specification teaches in Example 1 how this powerful technique is used to generate a methyltransferase with the desired activity. Each iteration of the novel assay described in Example 1 can screen about $10^9$ separate clones in only a few days (see page 40, lines 23-24, and page 41, lines 1-2, of the specification). Applicant maintains that Example 1 provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed and that the experimentation required is of a routine character. Furthermore, applicant maintains that the ability to quickly screen such a large number of clones provides a reasonable expectation of success in isolating a clone having the desired characteristics. Thus,

contrary to the Examiner's allegation, the quantity of experimentation needed to make and use the claimed invention is not large. Moreover, even if the quantity of experimentation were large, the experimentation would not be undue. It is the undue nature of experimentation, and not its quantity, which is incompatible with enablement.

Thus, the guidance provided in the specification in Examples 1 and 3 and the knowledge in the prior art, particularly with respect to phage-display selection of DNA binding proteins having the desired sequence specificity (see Desjarlais and Berg, 1993, Rebar and Pabo, 1994, and Wu et al, 1994, of record) demonstrate that, contrary to the Examiner's assertion, the experimentation required is not undue.

Finally, the Examiner rejected claims 44-46, directed to pharmaceutical compositions, because there is allegedly no evidence of record that the claimed composition can be used successfully to treat, prevent, or ameliorate any disease.

Applicant points out that the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. Applicant maintains that the Examiner has not provided a reasonable basis to question the enablement of the pharmaceutical compositions of claims 44-46.

In view of the above remarks, applicant maintains that claims 1-8, 10-15, 18, 24-26, and 42-46 satisfy the requirements of U.S.C. §112, first paragraph.

**Summary**

In view of the remarks made herein, applicant maintains that the claims pending in this application are in condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicant's undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the enclosed filing fee, is deemed necessary in connection with the filing of this Communication. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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